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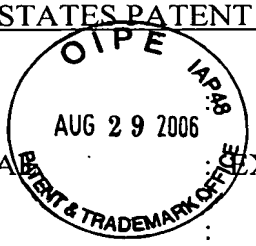


IN RE APPLICATION OF

STEPHEN ARKINSTALL, ET AL : EXAMINER: CHANG, CELIA C.

SERIAL NO: 10/088,090 :

FILED: JUNE 21, 2002 : GROUP ART UNIT: 1625

FOR: PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES :

SUPPLEMENTAL REPLY BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is in reply to the Supplemental Examiner's answer mailed June 29, 2006.

The New Matter Rejection under 35 USC 112, 1st paragraph

This rejection is simply untenable. The specification provides explicit, literal support for the definitions of the substituents set forth in Claim 1.

In maintaining this rejection, the Examiner has focused on one embodiment of the invention where it is stated that R^3 and R^4 must be an amino acid residue and the only other support for the species where R^3 and R^4 are hydrogen is found in reference to particular examples (see page 7 of the Examiner's Answer). This is, in fact, completely contrary to the specification.

First, as has been explained previously during in-person discussions with the Examiner, the term "amino acid residue" as representative of R^3 and R^4 in the compound of Claim 1 is understood as being the side chain of the amino acid (i.e., the portion of the amino

acid molecule that distinguishes one amino acid from another). Therefore, as is known in the art, the amino acid glycine, has hydrogen as a group that distinguishes from other amino acids, e.g., phenylalanine, and therefore provides support for hydrogen at R^3 and R^4.

Moreover, as stated numerous times previously, support for Claim 1 finds explicit, literal support on page 11, lines 10-25 reproduced again below (emphases added):

> In preferred sulfonyl amino acid derivatives **according to formula I**, **Ar^1 is an unsubstituted or substituted phenyl**, preferably a 4-chlorophenyl group, X is preferably O, R^1, R^2, **R^3 and R^4 are preferably hydrogen**, n is 1, Ar^2 is preferably thienyl, R^5 is H or C_1-C_6-alkyl.
>
> In said preferred embodiment, R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl-e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstiuted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl.
>
> The above mentioned aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxyl, nitro, acyloxy, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy.

For ease of reference, a Table had been previously provided which aligns the substituents set forth in Claim 1 and the above-noted portions of the specification supporting each of these substituents.

In addition, Appellants explained previously that there are specific examples provided in the specification that clearly demonstrate that the specification describes compounds within this generic disclosure on page 11. Examples 1, 4 and 6 describe species within the generic disclosure claimed.

Therefore, the specification clearly provides **explicit, literal support** for the formula defined in Claim 1.

There is no question that in view of the above facts, this ground of rejection should be REVERSED.

The Objection under 37 CFR 1.75(c)

The Examiner contends that there is no antecedent basis for R6 which is an alkyl substituted by heteroarylamino (see page 8 of the Examiner's Answer). This is simply incorrect.

Claim 1 can include as a substituent for R^6 a substituted C_1-C_6-aliphatic alkyl. Substituents are described on page 7, line 24 to page 8, line 10. Thus, support for the species listed in Claim 9 (as well as Claim 29) **is** found in the specification and find **proper antecedent** basis in the Claim 1.

There is no question that in view of the above facts, this ground of rejection should be REVERSED.

The Obviousness Rejection in view of U.S. '149

Claim 1 is patentable in view of U.S. patent no. 6,646,149 ("U.S. '149") because U.S. '149 does not provide any reasonable suggestion for the compounds claimed in Claim 1.

As discussed throughout the specification of U.S. '149, the only point of the discussion therein is to make and use polyamine compounds and derivatives of polyamines to inhibit polyamine transport and/or polyamine binding proteins. See Abstract and col. 1, lines 16-31; col. 6, lines 48-53 ("the present invention is directed to various polyamine analogues and derivatives"); col;. 7, lines 22-24 ("a polyamine analogue or derivative of the invention includes on that binds to a polyamine-binding site of a molecule and/or inhibits polyamine transport"); and col. 15, lines 40-43: noting the block noted on the right of the formula labeled "polyamine."

The U.S. '149 specification then goes on to list a laundry list of possible substituents the combinations of which appear to encompass thousands of possible compounds. What is central to all of the disclosure in this patent is the requirement of a polyamine so that the compounds can bind to polyamine transport and/or inhibit polyamine binding proteins (see above for citations).

The Examiner's reliance on compounds 1233 and 1241 on sheet 29 of the drawings of U.S. '149 is misplaced. The Examiner contends that the "art clearly taught the variation of a linker chain between the NR2 and the carbonyl moiety and the ordinary skill person was offered the concept of modifying 1233 with 1241 on the same page i.e. establishing a prima facie structural obvious." (page 10 of the Examiner's answer). First, the disclosure of two distinct compounds separate and apart from each other on the same page does nothing to suggest any modification. This simply seems like rationale for an unsubstantiated position.

Second, the U.S. '149 disclosure requires a polyamine group in the compounds which **polyamine derivatives [are] linked together via terminal amino groups** . . .see col. 15,

lines 31-34. The Examiner attempts to simplify the disclosure of U.S. '149 pertaining to the central and important polyamine moiety such that it is referred to as an amino-substituted alkyl (page 11 of the Examiner's Answer). However, the polyamine chain in U.S. '149 is 14 carbon atoms in length.

The compounds defined by formula I do not contain polyamine groups nor is there any guidance to select from this pointed disclosure in U.S. '149 to arrive at the compounds defined in Claim 1, noting that R6 can be a substituted C1 to C6 aliphatic alkyl (significantly different than a polyamine with 14 carbon/nitrogen atoms).

Third, as explained in the section of Appellant's Brief entitled "Summary of Claimed Subject Matter" the specification at page 9 states: "Quite surprisingly, it was now found that sulfonyl amino acid derivatives according to formula I are suitable pharmaceutically active agents, by effectively inhibiting the action of JNKs, notably JNK2 and 3." This statement is supported by data found in the specification discussed previously at page 32, lines 6-17; and page 34, lines 26-27.

Thus, this rejection should be REVERSED.

The rejection under 35 USC 112, 1st paragraph

There are two aspects to this rejection.

The first is based on the position of the Examiner that the compounds as defined in the claims are not adequately described—"the specification lacks the required sufficiency and guidance in supporting the claims, i.e. compounds having at least one of R3 and/or R4 is an amino acid possessing the 'critical role' in inhibiting JNK1, JNK2, or JNK3." (page 9 of the Examiner's Answer).

In essence, this is merely a restatement of the new matter rejection discussed above. For the reasons explained above, the specification unequivocally describes the compounds of formula I (again referring to the text at page 11). Moreover, as previously discussed in Appellants' Brief, the specification at page 13, line 24 – page 14, line 3 the describes how the compounds can be used; and on pages 15, 16 and 26-30 detailed guidance for making compounds of formula I are described. Therefore, the compound claims as well as the pharmaceutical composition containing the same are clearly enabled by the specification.

The second aspect of the rejection is based on the claims directed to the methods of using the compounds to (a) treat a disease of the autoimmune and/or neuronal system (e.g., Claim 30), (b) treat cancer (Claim 42), and (c) treat a cardiovascular disease.

The Examiner's statements in the Reply of June 29, 2006 on page 9 relating to the data on page 37 and 39 has completely ignored Appellant's previous statements (in the first Reply Brief and Supplemental Appeal Brief), that is the experiments previously discussed on pages 37 and 39 of the specification are prophetic examples and therefore any reliance on these examples as actual experiments is withdrawn in its entirety.

Claim 33 includes the phrase "to down-regulate or inhibit the JNK pathway," which as discussed previously is specifically discussed on page 5, lines 6-10 of the specification.

The method of using the compounds to treat a disorder of the autoimmune and/or neuronal system is described and enabled by the specification at page 13, line 24 through page 14, line 3.

In the *in vitro* data presented in the specification on pages 32 and 34, the ability of compounds representative of the claimed invention were shown to have JNK inhibiting activity. Thus, the specification establishes that the compounds of formula I inhibit JNK and since JNK plays a critical role in a variety of autoimmune and/or neuronal system, one would reasonably conclude that that the compounds can be used to treat a variety of disorders.

As described in the specification on pages 1-4, JNK (Jun kinase) act by its central involvement in crucial signaling pathways in the cell and as a result is integral to a number of pathways centered on expression genes, maintaining cell viability, and mediating signals from cytokines such as interleukin 2 and interferon. Furthermore, the specification describes that these activities are involved in a number of diseases and therefore by controlling the activity of JNKs one has the tool to treat these different disease states.

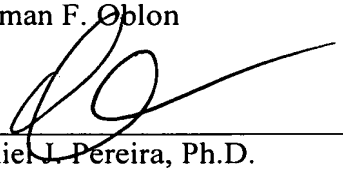
Accordingly and in view of the above, this rejection should be reversed.

Conclusion

Accordingly, in view of the above in combination with the reasons set forth in Appellants Appeal Brief of July 27, 2005, Reply Brief of December 2, 2005 and Supplemental Appeal Brief of April 17, 2006, all pending claims should be indicated as being allowed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Daniel J. Pereira, Ph.D.
Registration No. 45,518

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/03)